REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1, 5-7, 19-22, 24-29, and 31 are pending.

Claims 1, 5-7, 19-22, 24-29, and 31 were examined. Claims 1, 5-7, 19-22, 24-29, and 31 were rejected. No Claims were allowed.

No claims are amended herein.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Correspondence Address

The attorney of record is the undersigned (see Revocation and Power of Attorney, granting power to the undersigned, filed August 9, 2002 (copy enclosed). Applicants would be grateful for the Examiner's assistance in assuring that future correspondence is directed to current counsel, and not to prior counsel (Rothwell Figg).

Rejection under 35 U.S.C. § 112 - Written Description

Claims 1, 5-7, 20, 22-28 and 30 were rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled artisan that the inventors had, when the application was filed, possession of the claimed invention. This rejection is respectfully traversed.

The Office Action states that applicants have mischaracterized the Examiner's position. The Office Action further states that the instant specification fails to satisfy the written description requirement because "it does not provide any disclosure regarding critical relationship between structure and function . . . which is asserted to be a tumor marker and 'that binds Grb7' and which nucleic acids are expendable." (text bridging pages 5-6)

First, for the record, applicants did not intend to mischaracterize the Examiner's position, and express regret that the Examiner regards their response in such a manner.

To the substance of the rejection, applicants have provided an amino acid sequence of 2.2412 and have identified ankyrin-type repeats and additional repeat sequences within the protein (see, e.g.,

Fig. 1, and specification page 9, line 25 to page 10, line 2). These ankyrin domains were well known in the art, and were known to mediate protein-protein binding (see, e.g., specification page 9, lines 26-34). Moreover, the consensus sequence of ankyrin domains was known at the time of filing of the priority application and, in fact, was appreciated at least as early as 1993 (see, e.g., Bork Proteins. 1993 Dec;17(4):363-74, abstract attached). In addition, applicants identified other regions of the protein of particular note, such as the repetitive element, the stretch of serine residues, and the C-terminal region having a high content of charged amino acids.

Given this information, the ordinarily skilled artisan can readily determine where the 2.2412 protein can tolerate amino acid changes, including conservative amino acid changes. The specification provides guidance for such substitutions at, for example, page 5, line 34 to page 6, line 1). In addition, the ordinarily skilled artisan recognizes that, due to the degeneracy of the genetic code, nucleic acid sequence can tolerate changes that do not even affect the sequence of the polypeptide it encodes.

The Office Action also states that since the "specification fails to provide information regarding biological activity of the protein encoded by the claimed polynucleotides, one skilled in the art would not know 'how to assay for measuring the activity of the protein'" (page 6)

To the contrary, the specification describes a yeast two-hybrid assay to test binding of polypeptides to Grb7 family members, and further provides an example using Grb14 as "bait" (see, e.g., specification page 6, line 28 to page 7, line 23). An "activity of the protein" as claimed is binding to a Grb7 family member, which in the present claim is Grb7.

Finally, the Office Action states that "the instant specification provides no disclosure regarding nexus between 'binding to Grb7' and 'tumor marker", measurement of binding activity of protein with 95% identity to 2.2412 protein of SEQ ID NO:2, encoded by different claimed species of SEQ ID NO:1, clearly does not support analogy between instant case and the case disclosed in Example 14 [of the Utility Guidelines]."

This reasoning is not understood. The nexus between Grb7 binding and the polypeptide encoded by the claimed polynucleotide has been discussed above in the context of the characterization of the amino acid sequence of 2.2412. There is no requirement of a nexus between the structure and the asserted utility of use of claimed invention as a tumor marker – rather the requirement is that there exist a nexus among the species **of the claimed genus**. Applicants have provided this.

Applicants again urge that the Office consider that withdrawal of this written description rejection would provide applicants with a claim scope that is well within reason, the law, and the Office's own policy in applying the law. In particular, specifications having disclosure similar to that of the instant application have been deemed by the Office to support claims of such scope. Several patents have issued with claims reciting 95% sequence identity (see, e.g., U.S. Pat. No. 6,509,448). Other exemplary patents that have issued with such sequence identify language include U.S. Pat. Nos. 6,156,540; 6,506,587; 6,504,009; 6,503,733; 6,503,700; and 6,500,635. A search of the USPTO full-text database using the search strategy [aclm/sequence and aclm/identity and (aclm/amino or aclm/protein or aclm/polypeptide) and (aclm/75 or aclm/80 or aclm/85 or aclm/90 or aclm/95)] identified over 90 issued US patents, 26 of which have issued since 2002. To deny applicants of a similar claim scope is an inequitable and inconsistent application of the law.

In addition, and in the interest of a complete record, applicants maintain all applicable positions as presented in prior responses.

Accordingly, applicants respectfully request the withdrawal of this rejection.

Rejection under 35 U.S.C. § 101 - Utility

Claims 1, 5-7, 19-22, 24-29 and 31 stand rejected under 35 U.S.C. § 101 on the grounds that the claimed invention has no apparent or disclosed specific and substantial credible utility. This rejection is again respectfully traversed.

The Utility Examination Guidelines (Federal Register 66, No. 4, January 5, 2001; hereinafter "The Guidelines") provides instructions for examining patent applications for compliance with the utility requirement of 35 U.S.C. § 101.

The Guidelines state:

> "(a) ***If the applicant has asserted that the claimed invention is useful for any practical purpose*** (i.e., it has a "specific and substantial utility") ***and the assertion would be considered credible*** by a person of ordinary skill in the art, ***do not impose a rejection based on lack of utility***." (p. 1098, col. 1).

Applicants respectfully note that nowhere does the law require "evidence", as asserted in the Office Action. (page 3, last two paragraphs). Rather, the onus is on the Office to provide evidence that the

asserted utility is not credible. The Office has provided no such evidence that supports the Office's arguments that the asserted utility is not credible, and sufficient to meet the requirements of the law under 35 U.S.C. §101.

Furthermore, where an Applicant provides evidence rebutting an assertion of lack of utility, the Guidelines provide that:

> "Office personnel ***must*** accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; ***it is improper to disregard the opinion*** solely because of a disagreement over the significance or meaning of the facts offered". (p. 1099, col. 1).

Moreover, the Manual of Patent Examining Procedure (MPEP) elaborates on this issue in § 2107.02, which states the following:

> Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, ***unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement***.

(emphasis added)

The MPEP § 2107.02 also provides that "an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101." Accordingly, the Applicants maintain that if a utility is asserted in a patent application and that utility would be considered credible by one of skill in the art (termed herein a "skilled person"), then the claims must have patentable utility. Furthermore, if an opinion of an expert is offered as evidentiary support of an assertion of utility, e.g., by means of a Declaration under C.F.R. § 1.132, it cannot simply be ignored because it is contrary to the Office's position.

The Applicants maintain that the instant specification states that "detection of the encoded protein should provide a useful tumour marker and/or prognostic indicator" on page 1, lines 4-5. Since a "tumor marker" finds use as a diagnostic for cancerous cells, the Applicants respectfully submit that the claimed subject matter can be used as a cancer diagnostic.

As previously argued in the response filed on November 19, 2003, the asserted utility of the claimed subject matter is supported by, for example, a) post-filing publications (see e.g., Monz et al, Clin Cancer Res. 7:113-9, (2001), demonstrating that the claimed sequence is overexpressed in

meningiomas), and b) evidence in the form of a declaration by Dr. Hitoshi under 37 C.F.R §1.132, which provides gene expression data showing an association of 2.2412 with human cancers. Under the law, no more is required to satisfy the utility requirement of 35 U.S.C. § 101, and this rejection should be withdrawn without any further discussion. However, the Office maintains that the asserted utility is incredible in view of the factual evidence made of record.

Despite the arguments provided by Applicants as well as evidence in the form of a declaration, the Office still maintains that at the time of filing of the present application, a specific utility was not disclosed. With respect to the rejection, the Examiner states the following:[1]

> **However, the issue at hand in the instant case remains that at the time of filing, the instant specification fails to disclose the specific, emphasis added, and substantial credible utility of the instant novel interacting protein 2.2412 encoded by the claimed isolated polynucleotide molecules. As fully and extensively explained in the appropriate sections of the previous office actions, the assertion that a novel 2.2412 protein encoded by the claimed polynucleotide is a candidate effector protein for the Grb7 proteins, which maybe associated with cancer, does not make the instant DNA or encoded protein diagnostic of cancer.**

The Office's sole evidence to supports its case is that the instant specification provides no "evidence or sound scientific reasoning" (e.g., data) at the time of filing to support the claimed subject matter's utility as a tumor indicator.[2] This is not the standard. There is no such requirement in the MPEP, The Guidelines, or the law that requires "evidence or sound scientific reasoning" to be in a patent application to support an asserted utility.

The MPEP provides that "occasionally, an applicant will not explicitly state in the specification or otherwise assert a specific and substantial utility for the claimed invention in the specification...If the applicant subsequently indicates why the invention is useful, the Office personal should review that assertion according to the standards articulated below for review of the credibility of an asserted

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[1] Final Office Action, dated January 30, 2004, page 3.
[2] See, Office Action, dated August, 19, 2003, page 5 "The instant specification fails to provide any evidence or sound scientific reasoning to allow a conclusion.....", and "there is no disclosure that the claimed polynucleotides are expressed in

utility."[3] As such, the Applicants assert that the Examiner has failed to review the assertion of utility according to the standards presented in the MPEP, The Guidelines, and the law.

According to The Guidelines, all that is required to meet the utility requirement of 35 U.S.C. § 101 is a credible, specific and substantial utility – nowhere does it state that the utility must be evidenced or supported by "sound scientific reasoning" in the specification as filed.

Moreover, the MPEP provides that there is no predetermined amount or character of evidence that must be provided by the Applicants in support of an assertion of utility. Specifically, MPEP § 2107.02, provides the following guidelines in evaluating the evidence relating to utility provided by the Applicants:

> **the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt."** *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). **Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980) (reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response). See also *Rey-Bellet v. Englehardt*, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974) (data from animal testing is relevant to asserted human therapeutic utility if there is a "satisfactory correlation between the effect on the animal and that ultimately observed in human beings"). **Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.**[4]

(underline emphasis in original, bold emphasis added).

Accordingly, the Applicants respectfully submit that this rejection finds no basis in current law, and, accordingly, the Applicants maintain that this rejection should be withdrawn.

Applicants have further bolstered their position by submitting a Declaration by Dr. Hitoshi. The data provided in Dr. Hitoshi's Declaration clearly establishes that the claimed subject matter may be used to detect cancerous cells. This was acknowledged in the prior Office Action dated August, 19,

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altered levels or forms in any specific, diseased tissue.....", etc.

[3] MPEP § 2102.2, Section B "No Statement of Utility for the Claimed Invention in the Specification Does not Per Se Negate Utility."

[4] *See also In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d (BNA) 1578, 1583 (Fed. Cir. 1996).

2003.[5] However, the data introduced by Dr. Hitoshi's Declaration is being ignored by the Office solely on the grounds that it is produced subsequent to the filing date of the instant application and was not included in the application.[6]

However, the fact that Dr. Hitoshi's data was not included in the patent application is not relevant to the determination of utility. According to the MPEP, as noted above, an Applicant may later indicate why the invention is useful, where such assertion was not explicitly stated in the specification.[7] Once such an assertion is made, the MPEP then provides a series of guidelines in assessing the arguments and evidence provided by the applicant in support of the assertion.[8] Accordingly, the asserted utility remains the same, regardless of whether or not the assertion was included when the application was originally filed, or was later argued and supported by evidence.

In addition, the Declaration of Dr. Histoshi did more than provide data that supports the asserted utility of the instant application. Dr. Histoshi also reviewed the application, and pointed to specific statements in the application that provide a credible association of 2.2412 expression and human cancers.[9] Dr. Hitoshi, after reciting his understanding of what the specification recites, declares:

> **8. Given that 2.2412 specifically binds Grb14 and specifically binds Grb7, each which were known at the time the application was filed (September 23, 1997) to be differentially expressed in cancer cells compared to normal cells, it is reasonable to conclude that effectors for these proteins such as 2.2412 will also be differentially expressed (specification page 5, lines 13-16).**

In addition, Dr. Hitoshi concludes as one skilled in the art, that "in [his] opinion the '196 application sets out a credible association of 2.2412 expression in human cancers."

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[5] See Office Action, dated August, 19, 2003, page 6, "additional data show that 2.2412 was expressed at significantly higher levels in two types of lung cancer and three types of breast cancer".

[6] See, Office Action, dated August, 19, 2003, page 7, "Any further subsequent characterization of the claimed DNA and encoded protein, ...is considered to part of the act of invention.", "the instant specification, as filed, fails to provide any information regarding using novel 2.2412 sequences as specific markers for breast and lung cancer", and "there is no evidence of record in the instant specification, which specifically associates the instant DNA or encoded protein with any human cancers".

[7] See MPEP § 2102.2, Section B "No Statement of Utility for the Claimed Invention in the Specification Does not Per Se Negate Utility."

[8] See MPEP § 2102.2, Part III "Evaluating the Credibility of An Asserted Utility."

[9] Declaration of Yasumichi Hitoshi Under 37 C.F.R. §1.132, paragraph 9.

Moreover, the declaration of Dr. Hitoshi provides adequate support for the assertion of credible utility in reaching the conclusion that it is reasonable to conclude that the 2.2412 protein is differentially expressed in cancer cells based on analysis of statements in the specification relating to the interaction of 2.2412 protein with Grb7 and Grb14. In support of the assertions, Dr. Hitoshi provides results from experiments in which the expression of 2.2412 was studies in different cancer types and normal tissue. Based on the experiments Dr. Hitoshi concluded the following:[10]

> **14. The results of these studies are shown in Exhibit 3. As shown in the graphs, 2.2412 is expressed at significantly higher levels in two types of lung cancer (bronchioalveolar carcinoma and large cell carcinoma) relative to normal lung tissue. 2.2412 is also expressed at significantly higher levels in three types of breast cancer (invasive ductal carcinoma, intraductal carcinoma and invasive lobular carcinoma) compare to normal breast tissue.**

Dr. Hitoshi's conclusion that 2.2412 protein is differentially expressed in cancer is *independent of* and, in fact, *in spite of*, any of the statements to which the Office has repeatedly pointed as undermining the assertions of utility in the instant application. The Office is reminded that, under both case law and its own rules of practice, the Office is required to consider the factual evidence in the record, including the Hitoshi Declaration and its factual underpinnings, and either accept them as true or rebut them with a factual showing of its own.[11] Applicants request that such a factual showing be provided in an affidavit by the Examiner under 37 C.F.R. § 1.104(d)(2).

The scenario presented in this instance closely parallels the specific example provided on page 17 of the Revised Interim Utility Guidelines Training Materials,[12] which sets forth a hypothetical scenario, wherein claims were rejected because the Examiner believed the utility to be incredible, an expert Declaration was filed under C.F.R. § 1.132 to support the asserted utility, and the rejection was ***withdrawn***. For Examiner's convenience, the hypothetical on page 17 of the Revised Interim Utility Guidelines Training Materials is reproduced below:

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[10] Declaration of Yasumichi Hitoshi Under 37 C.F.R. §1.132, paragraph 14.
[11] *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d (BNA) 1578, 1583 (Fed. Cir. 1996).
[12] UNITED STATES PATENT AND TRADEMARK OFFICE, *Revised Interim Utility Guidelines Training Materials, available at* http://www.uspto.gov/web/offices/pac/utility/utilityguide (last visited April 29, 2003).

Attorney Arguments with Evidence (Alternative II)

Claim 2 has been rejected by the examiner under 35 U.S.C. § 101 and 35 U.S.C. § 112, ¶1. The examiner asserts that a credible utility has not been disclosed. Reconsideration under 37 CFR 1.111 is requested.

In support of applicants' statement of utility, attached hereto is a factual declaration under 37 CFR 1.132 by an expert with examples that unequivocally show that microbe X only gains entry into the cells of a host through the mucosa in the nose and mouth. The declaration also demonstrates that administering compound A blocks the mechanism by which microbe X enters the cells of the mucosa thereby preventing infection by the microbe. The only reasonable conclusion that could be reached based on the declaration and the fact that the statements made by the examiner are unsupported by evidence to the contrary is that preventing microbe X infection is, in fact, credible. For these reasons, the utility rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, should be withdrawn.

Examiner's Response to Attorney Arguments with Evidence (Alternative II)

The examiner should withdraw the utility rejections.

Accordingly, in view of the foregoing arguments and Dr. Hitoshi's declaration under 37 C.F.R. §1.132, the Applicants respectfully request that this rejection be withdrawn.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-012.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 30, 2004

By: _____
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Enclosures:
Bork Proteins. 1993 Dec;17(4):363-74 (PubMed abstract)
Revocation and Power of Attorney, granting power to the undersigned, filed August 9, 2002

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1: Proteins. 1993 Dec;17(4):363-74. Related Articles, Link

Hundreds of ankyrin-like repeats in functionally diverse proteins: mobile modules that cross phyla horizontally?

Bork P.

Max-Delbruck-Centre of Molecular Medicine, Berlin, Germany.

Based on pattern searches and systematic database screening, almost 650 different ankyrin-like (ANK) repeats from nearly all phyla have been identified; more than 150 of them are reported here for the first time. Their presence in functionally diverse proteins such as enzymes, toxins, and transcription factors strongly suggests domain shuffling, but their occurrence in prokaryotes and yeast excludes exon shuffling. The spreading mechanism remains unknown, but in at least three cases horizontal gene transfer appears to be involved. ANK repeats occur in at least four consecutive copies. The terminal repeats are more variable in sequence. One feature of the internal repeats is a predicted central hydrophobic alpha-helix, which is likely to interact with other repeats. The functions of the ankyrin-like repeats are compatible with a role in protein-protein interactions.

PMID: 8108379 [PubMed - indexed for MEDLINE]

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